

Special points of interest:

New FDA Med Watch

Alert: SGLT2 inhibitors

Drug Information Corner:

Cardiovascular effects of dapagliflozin

Welcome Pharmacy Resident Class of 2016!

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Pharmacotherapy Update

Editor Notes

This newsletter features members of the residency class of 2016, and is loaded with interesting and helpful information!

In this edition, you will read about a new dental clinic procedure, which will hopefully alleviate some of the frustrations experienced at the pick up window for medication orders.

You will also learn about a new agent for the treatment of type II diabetes from one of our pharmacy students. Could this agent provide cardiovascular benefit as well? You will have to read on to find out!

Several questions will be answered about metformin and its association with vitamin B12 levels thanks to a drug utilization review. A list of commonly asked questions is attached for your convenience along with recommendations with how to proceed in the future.

Finally, for some fun, find out where members of the Lebanon VA pharmacy either went, or are going, on vacation this summer.

Hope you are having a wonderful summer and enjoy this newsletter!

Jennifer James, PharmD, editor

Dina Hunsinger-Norris, PharmD, editor

New Dental Clinic Procedure

Dental Clinic Prescription Process

Dental patients who have just had dental surgery or hygiene patients on blood thinners who are picking up prescriptions at the pharmacy now have a new protocol to follow.

WHEN: Started 6/18/15

PROCEDURE: Once a patient has a completed procedure, the provider will enter the medication order(s) for pharmacy to process, noting that this is a “Dental Surgery Patient.” The patient will wait in the dental clinic area waiting room until the pharmacy calls the clerk in the dental office (x4768) to state the prescriptions are ready for pick up. At that point, the clerk will inform the patient, and hand him/her a pink permission slip, which has first priority in the pharmacy waiting queue, and have the patient proceed to the pharmacy for pick-up. The patient will report to the pharmacy kiosk, pick a ticket for “pink permission slip,” and once the number is called to the pharmacy window, will be handed the medication that is ready, as well as be counseled by the pharmacist. \*\*This is the same procedure the pharmacy uses for ASU (short procedure surgery unit)\*\*

Of Note for Window Pharmacist: Method of Pick up = “Dental Patient”

Of Note for Set-Up Pharmacist: Call clinic when finished and note contact name and time on batch label

*This will hopefully eliminate waiting times at the pharmacy and phone calls to the dentist/oral surgeon concerning orders not being entered prior to the patient’s arrival at the pharmacy.*

FDA Med Watch Alert!



SGLT2 inhibitors: Drug Safety Communication - FDA Warns Medicines May Result in a Serious Condition of Too Much Acid in the Blood

[Posted 05/15/2015]

AUDIENCE: Endocrinology, Family Practice

ISSUE: FDA is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. FDA is continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

BACKGROUND: SGLT2 inhibitors are a class of prescription medicines that are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. When untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease. SGLT2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine.

These medicines are available as single-ingredient products and also in combination with other diabetes medicines such as metformin.

RECOMMENDATION: Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change your diabetes medicines without first talking to your prescriber.

Health care professionals should evaluate for the presence of acidosis, including ketoacidosis, in patients experiencing these signs or symptoms; discontinue SGLT2 inhibitors if acidosis is confirmed; and take appropriate measures to correct the acidosis and monitor sugar levels.

Drug Utilization Review (DUR)



A recent DUR showed that low blood levels of cyanocobalamin (Vitamin B-12) may be a direct result of metformin therapy. The DUR showed that 84% of our veterans with an active prescription for metformin have not been screened for vitamin B-12 deficiency.

This issue is important because B-12 deficiency-induced neuropathy can be reversible with B-12 supplementation, but may be mistaken for diabetic neuropathy and may lead to permanent neurological damage if left untreated.

Recommendations for B-12 monitoring/supplementation based on DUR results:

- Order a yearly B-12 level for patients taking metformin
- If B-12 level < 200 pg/mL, order supplemental B-12
- If B-12 level 200-300 pg/mL, or if patient is experiencing neurological signs/symptoms (eg. dementia, weakness, sensory ataxia, paresthesia), consider ordering serum methylmalonic acid (MMA) level to help rule out clinically significant B-12 deficiency. Keep in mind that other potential causes of MMA elevation should be corrected if possible prior to initiating therapy (hypovolemia, renal insufficiency, inherited metabolic defects)

Interpreting lab results:

MMA level elevated → B-12 deficiency possible  
MMA normal → B-12 deficiency unlikely

(continued on page 6)

# Drug Information Corner: Cardiovascular Effects of Dapagliflozin

By Trina Patel, Wilkes PharmD Candidate Class of 2016

Dapagliflozin (Farxiga) is a sodium glucose co-transporter 2 (SGLT2) that was recently approved by the FDA in January of 2014 for type 2 diabetes. On April 7th, 2015 there was an article published in Diabetes Care that discussed a trial that looked at dapagliflozin’s safety and efficacy. It was a 24 week multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension period funded by National Institute of General Medical Sciences of the National Institutes of Health. Patients were stratified by cardiovascular events (more than or less than 1 year), age (greater than or less than 65 years), and insulin use. The primary end points were the following: average change in HbA1c level from baseline to week 24 and the portion of patients who achieved the three-item endpoint. The three-item endpoint included: absolute drop of HbA1c from baseline (>0.5%), relative drop for total body weight (>3%), and absolute drop in seated systolic blood pressure from baseline (>3mmHg).

Of the 922 patients with a pre-existing cardiovascular event, hypertension, and type 2 diabetes, 807 completed the 52 week study. Of the 115 patients that did not complete the study, their reasons for incompletion were mainly due to: adverse events, withdrawal, non-compliance, and loss to follow up. Adverse events experienced in the study included: hypotension, fungal genital infection, neoplasms, and renal failure/impairment, which were more commonly seen in the dapagliflozin group than placebo. The results of the study demonstrated a reduction in mean HbA1c that was statistically significant for the patients on dapagliflozin compared to the placebo group at week 24 (average reduction of 0.38%) and maintained at week 52. The three-item endpoint was also proven statistically significant in the dapagliflozin group compared to the placebo.

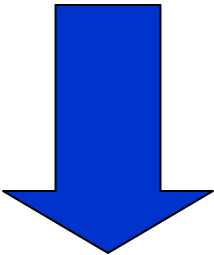
As with any trial, there can be limitations and strengths. Limitations include possible bias from AstraZeneca (the company that makes dapagliflozin) and their employees since they contributed to the study concept, design, analysis, and interpretation of the data. Also, the patients studied were mainly white. There were few Black patients which, if more were included, the results (three-item endpoint specifically SBP) could have been different. Another limitation was that the article did not discuss power. This would be important to address because if the study met power it would reduce type 2 error. Lastly, the mean baseline HbA1c was around 8%, making it unclear if patients with higher baseline HbA1c will have a greater reduction in HbA1c on dapagliflozin. Strengths of the trial include the study design, intention to treat analysis, and the fact that the study addressed co-morbid conditions (cardiovascular disease).

Overall, the author concluded that dapagliflozin is better at reducing HbA1c levels, body weight, and systolic blood pressure than placebo in patients with type 2 diabetes, hypertension, and cardiovascular disease. With this trial, the safety and efficacy of dapagliflozin is still unknown long term. There is another study, the DECLARE study, currently in process to help clarify this unknown. The study began in 2013 with 17,150 patients, and is a randomized placebo trial that will conclude in April 2019. The study is looking at the long term effects of dapagliflozin compared to placebo, and focusing on the endpoints of cardiovascular death, myocardial infarction, ischemic stroke, and malignancies (since dapagliflozin may be linked to bladder cancer).

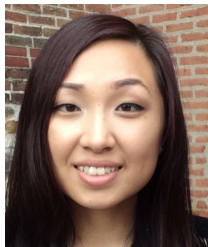
Therefore, although the article proved dapagliflozin may have cardiovascular benefits, more long term information needs to be gathered before it can be a valid option for patients in clinic today. Also, as of now the drug is a very expensive option since it is still fairly new. When the DECLARE trial concludes, and if dapagliflozin is shown to be safe and effective, then this drug would be a good option as additional therapy to metformin or a sulfonylurea for many patients with type 2 diabetes at the VA, especially if it becomes less expensive in the future.

References:

1. Article: Bruin TWA, Cefalu WT, Leiter LA, et al. Dapagliflozin’s effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. Diabetes Care [journal on the internet]. 2015 Apr 7 [cited 2015 May 29] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25852208>
2. Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58). ClinicalTrials.gov [internet]. 2015 June 22 [cited 2015 22 June] Available from: <https://clinicaltrials.gov/ct2/show/NCT01730534>



## Welcome Pharmacy Resident Class of 2016!



### Jinsun Paek, Pharm. D., PGY-2 Administration Resident

**Nickname:** Jin      **Hometown:** Mount Pocono, PA      **Pharmacy School:** USciences  
**PGY1 Location:** St. Luke's University Health Network, Bethlehem PA  
**Hobbies:** Running, baking, cooking, eating  
**Current Music:** Maroon5 Sugar  
**Favorite vacation destination:** Anywhere with hiking trails, lakes —> Dream vacation is Hawaii  
**Fun Fact:** I have an eggplant allergy



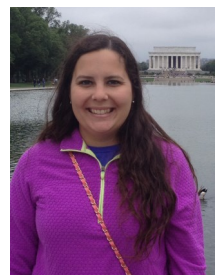
### Janki Shah, Pharm. D., PGY-2 Ambulatory Care Resident

**Nickname:** Janu      **Hometown:** Totowa, NJ      **Pharmacy School:** UConn  
**PGY-1 Location:** Lebanon VA Medical Center—Lebanon, PA  
**Hobbies:** Listening to music, reading  
**Current Music:** Pentatonix, Lindsey Sterling  
**Favorite Vacation Destination:** San Diego, CA  
**Fun Fact:** Can rap with Nicki Minaj



### Jennifer James, Pharm. D., Non-Traditional PGY-1 Pharmacy Resident

**Nickname:** Jen      **Hometown:** Hummelstown, PA      **Pharmacy School:** LECOM  
**Hobbies:** Running, cooking, hiking, jet skiing, boating, snow mobiling  
**Current Music:** Mandisa  
**Favorite vacation destination:** Kefalonia, Greece  
**Fun Fact:** I've run a half marathon and two full marathons in a matter of 3 weeks (and will never do that again)!



### Emalee Hribick, Pharm. D., PGY-1 Pharmacy Resident

**Nickname:** Ema, Em      **Hometown:** Lititz, PA      **Pharmacy School:** Temple University  
**Hobbies:** dancing, swimming, hiking, biking, camping, snowboarding, baking  
**Current Music:** Taylor Swift and country music  
**Favorite Vacation Destination:** Naples, FL  
**Fun Fact:** Was a lifeguard at Mt. Gretna Lake for 6 years  
**Misc:** I love chocolate!



### Morgan Peterman, Pharm. D., PGY-1 Pharmacy Resident

**Nickname:** Morg      **Hometown:** Curwensville, PA      **Pharmacy School:** Wilkes University  
**Hobbies:** Running, eating, shopping, and traveling  
**Current Music:** Last Pandora station was Florence and the Machine  
**Favorite Vacation Destination:** Dominican Republic, back-packing through Europe is on the bucket list  
**Fun Fact:** Day 3 and already had to go to employee health  
**Misc:** I'm obsessed with my dog who unfortunately lives with my parents.



### Jennifer Sobeck, Pharm. D., PGY-1 Pharmacy Resident

**Nickname:** Jenn      **Hometown:** Harveys Lake, PA      **Pharmacy School:** Wilkes University  
**Hobbies/Favorite Activities:** I like to read, scrapbook, bake, watch HGTV design shows (my favorite is Fixer Upper)  
**Current Music:** The last CD I bought was Kelsea Ballerini  
**Favorite Vacation Destination:** Favorite island visited as part of a cruise was Bermuda and would love to go back  
**Fun Fact:** I'm a Licensed Zumba Instructor

Where did you go, or where will you be going, on vacation this summer?!



1. Tony Sniechoski

2. Elisa Breeze-Knox

3. Deborah Miskie

4. Ed Moldenhauer

5. Christy Dayhoff

6. Keith Vinglinsky

7. Inga Washington

8. Morgan Peterman

9. Janki Shah

10. Robbie Janoszek

11. Steven Miller

12. Michele Margut

13. Heather Ulrich

14. Jody Boyer

15. Paul Carnes

16. Jennifer James

17. Virginia Jordan

18. Lou Portas

19. Jennifer Sobeck

20. Lindsay Baun

21. Brian Murray

22. Monica Bowen

23. Wendy Meginley

24. Stephen Harkaway

25. Agot Agot

26. Emalee Hribick
- A. Poconos

B. Thousand Trails

C. OCMD

D. Philadelphia, PA

E. Lake Raystown

F. Costa Rica

G. Wildwood, NJ

H. Europe

I. Manchester, NH

J. Corolla, NC

K. Des Moines, IA

L. Topsail, NC

M. Lebanon, PA

N. Cape May, NJ

O. Croatia

P. Outer Banks, NC

Q. Louisville, KY

R. England

S. Tennessee

T. Europe

U. OCMD

V. Hershey Park

W. Virginia Beach, VA

X. Lititz, PA

Y. North Dakota

Z. San Antonio, TX

1. T 2. W 3. Q 4. X 5. Z 6. G 7. Y 8. C/U 9. I 10. B 11. O 12. E 13. P 14. C/U 15. V 16. H/T 17. A 18. M 19. D 20. F 21. J 22. S 23. L 24. H/T 25. K 26. N

Continued from page 2: DUR of Metformin and Vitamin B12

Supplemental B-12 recommendations:

B-12 may be supplemented with daily oral therapy (1000-2000mcg) or periodic intramuscular (IM) therapy (1000mcg). Typically, IM therapy is used initially to quickly correct deficiency and oral therapy may be used for maintenance therapy, though IM therapy may also be used for maintenance and may be preferred if lack of compliance with daily oral therapy is a concern.

Metformin and Vitamin B-12 FAQ:

What is the relationship between metformin therapy and vitamin B-12 levels?

It has been demonstrated that metformin may induce vitamin B-12 malabsorption, which may increase the risk of developing vitamin B-12 deficiency.

Why is this potential vitamin B-12 deficiency of special concern?

Vitamin B-12 deficiency may lead to neurological damage that might first present as peripheral neuropathy and may be reversed with supplementation of vitamin B-12. Vitamin B-12 deficiency-induced peripheral neuropathy may be mistaken for diabetic neuropathy, and if left untreated may lead to irreversible neurological damage.

My patient is on a low dose of metformin, do I still need to worry about vitamin B-12?

Studies have suggested that the greatest risk factors for metformin-induced vitamin B-12 deficiency are a high dose of metformin (2000-2550mg/day) and long-term therapy (> 3 years). Patients who are on a high dose or have been taking metformin for > 3 years should be screened for B-12 deficiency.

My patient has been on metformin therapy for > 3 years and has had a normal B-12 level each year. Should I still keep monitoring B-12?

Metformin-induced B-12 deficiency may take up to 15 years to develop, so it would be prudent to continue monitoring B-12 levels yearly.

My patient’s B-12 level is on the lower end of normal, is supplementation still needed?

The normal range for a B-12 level in CPRS is listed as 108-963 pg/mL, however patients may have clinically significant B-12 deficiency even if they are within the normal range.

Is there a way to see if a B-12 level that falls on the lower end of normal signifies clinically significant deficiency?

A serum methylmalonic acid (MMA) level may help confirm the presence/absence of a B-12 deficiency if the B-12 level is within the normal range and:

- A patient is exhibiting neurological signs/symptoms (eg. dementia, peripheral neuropathy)
- A patient may be more likely to have a deficiency (elderly, alcoholics, malnourished)
- A patient is anemic (folate levels should be considered as well if patient anemic)
- A patient’s B-12 level is 300 pg/mL or below

What is the best way to supplement vitamin B-12?

B-12 may be supplemented with daily oral therapy (1000-2000mcg) or periodic intramuscular (IM) therapy (1000mcg). IM therapy should be used initially to quickly correct deficiency and oral therapy may be used for maintenance therapy, though IM therapy may also be used for maintenance and may be preferred if lack of compliance with daily oral therapy is a concern.

Additional Resources:

- Pierce SA, Chung AH, Black KK. Evaluation of vitamin B12 monitoring in a veteran population on long-term, high-dose metformin therapy. Ann Pharmacother. 2012 Nov;46(11):1470-6.
- Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Arch Intern Med. 1999 Jun 28;159(12):1289-98.

